

REMARKS

With the entry of the present Amendment, Claims 1, 4-6, 8-23, 37 and 40-44 are in this application; claims 1-6, 8-11, 13, 19-23, 37 and 40-44 have been examined. Claims 2-3, 7, 24-26 and 38-39 have been canceled without prejudice. Claims 1, 6 and 19 have been amended to recite that the peptide inhibits SARS virus infectivity. Claim 1 has been amended to incorporate the limitations from claims 2-3. Support is found in as-filed claim 2, for example. Claims 10, 37 and 40-44 have been amended to better claim the invention. New claim 45 has been presented; it is supported by as-filed Fig. 17A. None of the amendments made herein constitutes the addition of new matter.

The Rejection under 35 U.S.C. 103

The Patent Office has requested confirmation that the subject matter of the various claims was commonly owned at the time the invention was made. Applicants confirm that the subject matter of the various claims was commonly owned at the time the invention was made.

Claims 1-6, 8-11, 13, 19-23, 37 and 40-44 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Rottier (US 2004-0071709, filed April 14, 2003) in view of Kliger et al. (2003) BMC Microbiology 3:20. Applicants respectfully traverse this rejection.

The Patent Office has indicated that the cited Rottier reference teaches a 49 amino acid peptide derived from SARS CoV (Tort2), which peptide comprises a continuous sequence of 14 amino acids of SEQ ID NO:67 of the present claims. In the stretch of sequence provided, it is said that there is only one amino acid difference between amino acids 1-36 of instant SEQ ID NO:67 and amino acids 7-42 of Rottier's SEQ ID NO:27. Rottier is said to teach that S proteins of SARS-CoV possess an α -helical trimeric conformation and that HR2 peptides of SARS can inhibit anti-parallel coiled coil formation of a coronavirus spike protein by decreasing contact between heptad repeat regions of the protein. They are further said to be potent antivirals.

Rottier was characterized above and is said to further teach HR2 sequence homology between DR2 of SARS-CoV and those of other coronaviruses. The Kliger reference is said to teach the C-terminal HR sequence, with reference to Fig. 3b, and Kliger is said to show the helical wheel of C-HR.

The Examiner has drawn on the KSR Supreme Court decision, alleging that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to make the HR-C4 analog of SEQ ID NO:67 by substituting Ile for Ala in order to make a more stable helix structure. The Examiner has further alleged that there would have been a reasonable probability of success in obtaining an analog, like that of SEQ ID NO:67.

Applicants respectfully submit that neither the cited Rottier reference nor Kliger teach or suggest that a peptide shorter than 47 amino acids would be useful in preventing SARS virus infection or that any or all of such peptides would be effective in blocking or inhibiting infection of cells. Applicants do not see what in the cited references would lead one to change the particular Ala residue to Ile as in SEQ ID NO:67 or why one would have the goal of improving helicity. Neither do these references lead one to suspect that doing so would produce an inhibitor of SARS infection (or a useful immunogenic sequence). In Paragraph [0091] of the cited Rottier reference, it is stated that peptides HR1, HR1a, HR1b, HR1c and HR2 were tested for their abilities to inhibit virus entry into cells and of these, **only HR2** "blocked viral entry in a concentration-dependent manner". However, the Examiner is correct that Fig. 10 shows a comparison of the HR2 of several viruses and there is **some** relatedness to SEQ ID NO:67. Please note that it is Applicants' position that the teachings of the cited reference do not clearly lead the skilled artisan to the particular region of the S protein modified to produce an inhibitor of virus infection, the inhibitor being a peptide of from about 14 to about 35 amino acids, with any reasonable probability of success.

In fact, none of the regions of the S protein pointed out in Rottier's Figure 1B correspond to the 1147-1185 region of the protein corresponding to the HR-C peptide of the present application. Thus, Rottier would lead the skilled artisan away from the present claimed invention in that it focuses on other portions of the S protein than those regions of importance in the present application, for example, in the generation of SEQ ID NO:67 and others recited in the present claims. Similarly, the 909-957 region of the S protein used to create the HR-N peptides is not a region highlighted by Rottier in his Fig. 1B. Again, this should properly be construed as teaching away, or at a minimal, as not pointing to the "lead" starting materials in the present Specification and claims, as related to HR-N or to HR-C peptides and their analogs.

Moreover, a direct comparison of present SEQ ID NO:67 with the MHV HR2 sequence shows, over the aligned length of 36 amino acids, there were only 12 identical residues (about 33%). A comparison of SEQ ID NO:67 with the FIPv sequence reveals that there are only 8 residues identical in the aligned 36 amino acid sequence (less than 25%). Applicants do not see how this reference points the skilled artisan to the particular region of the protein or to a particular residue for change, i.e. the Ala to Ile substitution in the native SARS sequence at position 23. Given the large number of differences at a number of amino acid positions in the HR2 subregion related to SEQ ID NO:67, Applicants respectfully submit that position 23 is not called out as a particular amino acid of interest, given the overall differences in sequence. There is not a clear indication that the state of the art would have led one of ordinary skill in the art to the present claimed invention, when there are many other alternatives that could have been generated.

As to the cited Kliger reference, Applicants believe it is best viewed as **speculative**: See the paragraph at fourth page, bottom right, where it is said "[p]eptides derived from the C-HR segment of SARS-CoV S2 protein... **might** inhibit viral induced membrane fusion, thereby blocking SARS-CoV infection" [emphasis added]. Comparing this sequence with the viral sequences in Fig. 10 of Rottier does not lead one to the particular **Ala to Ile** change embodied in SEQ ID NO:67. The cited Kliger

reference does not supply what it is absent from the teachings of the Rottier reference, and it is Applicants' position that the general state of the art would have led the ordinarily skilled artisan to do what the present inventors have done. Similarly, the peptide of SEQ ID NO:111 also contains the Ala to Ile change as well. Rottier appears to make no teaching or suggestion of a vaccine or other immunogenic composition comprising any natural or engineered peptide derived from the SARS S protein.

In response to Applicants' prior arguments, the Patent Office has countered that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference, nor is it that the claimed invention must be expressly suggested in any or all of the cited references, but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. The Examiner has stated that the scope of the instant claims relates to a genus of peptides capable of inhibiting SARS infectivity. Rottier teaches the use of peptides corresponding to the HR region of SARS as inhibitors, including a 49 amino acid peptide of SEQ ID NO:27 and Kliger suggests peptides corresponding to C-HR. These peptides of the prior art are said to be functional equivalents of SEQ ID NO:67 and that there was a reasonable expectation of success in obtaining peptides of 14-35 amino acids in length.

Applicants respectfully point out that the present specifically claimed peptide of SEQ ID NO:67 is **not** a functional equivalent of the prior art peptide of Rottier or Kliger. Note that the present Specification teaches that the peptide of SEQ ID NO:67 has **greater** tendency to maintain a helical conformation. This is a functional attribute which is counter to the allegation that the instant claimed peptide is a functional equivalent of the peptide of the prior art.

Applicants review the mechanism for entry of the SARS virus into susceptible cells, at least in part. For infection to occur, the three "C" bundle helices must re-associate and interact with a 3 helix "N" bundle of the protein to form a C₃N₃ "superbundle", i.e. a six-helix heterotrimer. If the C bundle made with a variant peptide

that associates in this bundle in a more stable fashion than the wild type peptide, then one of ordinary skill in the art would have expected that this stable C bundle would be less likely to dissociate than the wild type equivalent so as to allow the formation of the C₃N₃ superbundle involved in entry. In other words, one would not have expected the Ile variant to be a good inhibitor of virus entry because it would have been expected that the C3 bundle, which is essential for fusion, would have been thermodynamically favored over the superbundle. In other words, it is not to be expected that peptides in a helical conformation would be able to compete with the viral S protein helical regions in order to inhibit infection. Thus, Applicants respectfully maintain that the Examiner is incorrect in the position that it would have been obvious to make the particular Ala to Ile change like that of the peptide of SEQ ID NO:67 to achieve the intended result.

Applicants respectfully note that with respect to the Ile residue in SEQ ID NO:67, there is nothing in either cited reference which would lead the skilled artisan to this particular peptide sequence, when as discussed above, there are numerous amino acid differences between that claimed peptide and those of the cited art. The Ile analog (i.e. SEQ ID NO:67) is more stable in the helical configuration than the corresponding Ala sequence (the natural sequence derived from the SARS spike). It was a **surprising** result that this derivative worked so well to inhibit SARS entry into cells, a critical part of the infection process. Conventional wisdom would hold that the Ala sequence would have been a better peptide for use in making a SARS-inhibiting antibody. In other words, a peptide with increased C bundle stability would not have been seen as a good candidate for inhibiting SARS entry prior to present Applicants' invention and disclosure.

Claim 37 and new claim 45 relate to immunogenic compositions. Neither Rottier nor Kliger appear to teach the use of any SARS virus S protein peptides for generating an immune response. In addition, note that the peptides specifically recited by SEQ ID NO in claim 45 contain differences from the native HR-C and HR-N sequences and the HR-C or HR-N derived segments are flanked by artificial sequences which are specifically designed to optimize presentation of the internal segment to the immune system and to allow disulfide bond formation using the teachings of Fig. 17A-17B. This

is not obvious to one of ordinary skill in the art based on the cited references, even taking into account the general knowledge in the art.

In view of the foregoing, Applicants respectfully maintain that the present invention as claimed is not *prima facie* obvious over the cited references, and the rejection under 35 U.S.C. 103 should be withdrawn.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Request for Continued Examination, a Petition for Extension of Time and payment of the fees due pursuant to 37 C.F.R. 1.17. It is believed that this amendment does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If this is incorrect, however, please grant any further extension of time, if needed, and charge the appropriate amount due under the foregoing Rules to Deposit Account No. 07-1969.

Respectfully submitted,

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